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Corporate Medical Policy

Molecular Markers in Fine Needle Aspirates of the Thyroid
AHS - M2108

File Name:	molecular_markers_in_fine_needle_aspirates_of_the_thyroid
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Description of Procedure or Service

Fine needle aspiration - tissue samples are obtained for cytologic examination using 23 to 27 gauge (commonly 25 gauge) needles with or without local anesthesia. (Ross, 2017).

Mutation analysis – Mutational analysis by sequencing or PCR which identifies individual molecular markers of malignancy including *BRAF*, *RAS*, *RET*/*PTC*, and *PAX8*/PPARgamma (Ross, 2017).

Gene expression classifier – measures mRNA to determine the activity level of a panel of 167 genes and uses an algorithm to predict malignancy based on gene expression (Ross, 2017).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for molecular markers in fine needle aspirates of the thyroid when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Markers in Fine Needle Aspirates of the Thyroid is covered

The use of molecular markers in fine needle aspirates of the thyroid is considered **medically necessary** for the following:

- Mutation analysis (Eg. BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or the use of gene expression classifier (Eg. Afirma GEC) in fine-needle aspirates of the thyroid that are cytologically characterized as follicular cell neoplasm (FN) / suspicious for follicular neoplasm (SFN), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) in adult patients (>18 years of age) being evaluated for thyroid carcinoma to assist in patient management decisions.

When Molecular Markers in Fine Needle Aspirates of the Thyroid is not covered

The use of molecular markers in fine needle aspirates of the thyroid is considered **investigational** for the following:

A. Mutation analysis (Eg. BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or the use of gene expression classifier (Eg.Afirma GEC) in fine-needle aspirates of the thyroid that are cytologically characterized as Hurthle cell, papillary or anaplastic neoplasm in adult patients (>18 years of age) being evaluated for thyroid carcinoma.
B. Mutation analysis (Eg. BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or the use of gene expression classifier (Eg.Afirma GEC) in fine-needle aspirates of the thyroid that are cytologically characterized as follicular or Hurthle cell neoplasm (FN) / suspicious for follicular neoplasm (SFN), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), papillary or anaplastic neoplasms in pediatric patients (≤ 18 years of age) being evaluated for thyroid carcinoma.
C. The microRNA profiling tests (Eg.RosettaGX Reveal) in fine-needle aspirates of the thyroid that are cytologically characterized as follicular or Hurthle cell neoplasm (FN) / suspicious for follicular neoplasm (SFN), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), papillary or anaplastic neoplasms in adult (>18 years of age) and pediatric (≤ 18 years of age) patients being evaluated for thyroid carcinoma.
D. Mutation analysis (Eg. BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or the use of gene expression classifier (Eg.Afirma GEC) or the microRNA profiling tests (Eg.RosettaGX Reveal) in adult (>18 years of age) and pediatric (≤18 years of age) patients in all other situations.

Policy Guidelines

Fine-needle aspiration (FNA) is a traditional diagnostic approach to differentiate thyroid nodules that are malignant and need to be treated surgically from the majority of nodules that are benign and do not require surgery. It offers definitive diagnosis in the majority of cases, however, 10–25% of nodules yield an indeterminate cytologic diagnoses, in which cancer cannot be ruled out, leading to suboptimal management of these patients and frequently resulting in unnecessary surgical interventions (Nikiforov, Yip, & Nikiforova, 2013). The risk of malignancy with these cytologic classifications ranges from 5 to 32 percent (Ross, 2017).

There are three main types of thyroid carcinoma: the differentiated, medullary and anaplastic. The differentiated histologic types of thyroid carcinoma include papillary, follicular or Hurtle cells. The anaplastic carcinoma is an aggressive, undifferentiated tumor which is almost uniformly lethal. Differentiated thyroid carcinoma are usually asymptomatic. They are commonly detected as solitary nodule. And, their evaluation is difficult because benign nodules are prevalent and thyroid carcinoma is uncommon (Mazaferri, 1993).

The FNA results are normally categorized according to NCI (Cibas and Ali, 2009) into the following categories: carcinoma (papillary, medullary, or anaplastic) or suspicious for carcinoma; follicular or Hurtle cell neoplasm; atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); thyroid lymphoma; or benign.

Three approaches to detection of molecular markers from fine needle biopsy of thyroid nodules have been developed based on mutational and other molecular markers, which can be reliably detected in cells aspirated during the FNA procedure (Hodak & Rosenthal, 2013; Xing, Haugen, & Schlumberger, 2013).

A study of *BRAF*, *RAS*, *RET*/*PTC*, and *PAX8*/PPARgamma mutational analysis, reveals that detection of any mutation conferred a risk of histologic malignancy of 88 and 87 percent for samples showing FLUS/AUS and follicular neoplasm, respectively (Nikiforov et al., 2011). However, a 14 percent false negative rate limits the usefulness of this panel.

Expanding to using a next-generation sequencing assay, additional point mutations (including *TERT*, *TP53*, and others), as well as gene fusions that occur in thyroid cancer (Nikiforov et al., 2014) result in a negative predictive value for malignancy of 96 percent and a positive predictive value of 83 percent for cytology showing follicular neoplasm.

Using mRNA expression analysis and a gene expression classifier trained on FNA samples to detect benign thyroid nodules, the classifier had a negative predictive value for malignancy of 95 percent but the positive predictive value was only 38 percent, respectively(Alexander et al., 2012; Chudova et al., 2010; McIver et al., 2014).

A combined test using both miRNA gene expression combined with mutational analysis had a negative predictive value of 97 and 91 percent and a positive predictive value for malignancy of 68 and 82 percent, respectively (Labourier et al., 2015).

No one methodology has achieved clinical utility to reliably resolve all indeterminate cytology, and thus several professional organizations, including the American Association of Clinical Endocrinologists (AACE)(Gharib et al., 2016) and the American Thyroid Association (ATA)(Haugen et al., 2016), National Comprehensive Cancer Network (NCCN)(NCCN, 2016), have published guidelines for the evaluation of thyroid nodules, all of which endorse a similar multistep strategy suggesting molecular markers can be of use when cytology is indeterminate yet acknowledging its current limitations.

Commercially available panels of molecular markers utilizing FNA specimens from the thyroid include the following tests:

ThyGenX and ThyraMIR

ThyGenX (Interpace Diagnostics, Parsippany, NJ) is a specific oncogene, mutational panel that is testing genetic alterations across 8 genes associated with papillary carcinoma and follicular carcinoma. ThyGenX uses next generation sequencing platform to identify genetic alterations across those 8 genes. The only cases accepted for ThyGenX testing are those that are identified as AUS/FLUS or FN/SFN. Recently, Interpace Diagnostics has developed a new molecular test, ThyraMIR. This test is based on the microRNA analysis. It is a microRNA Gene Expression Classifier that analysis the expression of 10 microRNAs. The manufacturer claims that this test can identify malignancy in nodules that are negative for ThyGenX. According to Interpace Diagnostics, combined test performance has negative predictive value of 94%, positive predictive value of 74%, with 89% sensitivity and 85% specificity.

ThyroSeq v3

ThyroSeq is a test intended for assessment of thyroid nodules with undetermined cytology initially designed to target 12 cancer genes with 284 mutational hotspots. The latest version of this test ThyroSeq v3 is based on next-generation sequencing of DNA and RNA. This test analyzes 112 genes, providing information on more than 12,000 mutation hotspots and more than 120 gene fusion types. In a multicenter study, this test was able to produce negative predictive value of 97%, positive predictive value of 66%, with 94% sensitivity and 82% specificity in 247 cases.

In addition to ThyroSeq test, other formats of NGS-based molecular tests for thyroid nodules are offered by others.

Affirma GEC

The Afirma "Gene Expression Classifier" (GEC) is a proprietary diagnostic test offered by Veracyte (Veracyte Inc, South San Francisco, California), which claims to classify a thyroid nodule with indeterminate cytology as benign (with >95 percent negative predictive value) or as suspicious for malignancy (>50 percent risk of malignancy). The GEC measures the mRNA expression of 167 different genes. In the total number of 167 genes tested, a set of 25 genes represents less common entities seen in the thyroid and the second set of 142 genes represents the most common thyroid entities. They only accept FNA lesions that are designated as FLUS/AUS and suspicious for Hurthle/follicular neoplasm.

RosettaGX Reveal

The RosettaGX Reveal test from Rosetta Genomics is a mcro-RNA-based diagnostic test that evaluates cytologically undetermined thyroid nodules. The test has a claimed negative predictive value of 99% with 98% sensitivity.

Applicable Federal Regulations

Commercially available panels of molecular markers utilizing FNA specimens from the thyroid are currently considered to be a laboratory-developed tests.

These commercially available, laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines for thyroid carcinoma (NCCN, 2017) state: "Molecular diagnostic testing to detect individual mutations (e.g., BRAF V600E, RET/PTC, RAS, PAX8/PPAR [peroxisome proliferator-activated receptors] gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions". They further clarify that, "The choice of the precise molecular test depends on the cytology and the clinical question being asked. Indeterminate groups include: 1) follicular or Hurthle cell neoplasms; and 2) AUS/FLUS." The NCCN panel recommends molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS (category 2A) and does not recommends this testing for suspected Hurthle cell neoplasms. The NCCN Panel further recommended (category 2B) "molecular diagnostic testing for evaluating FNA results that are suspicious for: 1) follicular or Hurthle cell neoplasms; or 2) AUS/FLUS."The NCCN panel emphasizes on the caution for the interpretation of molecular markers because they should be interpreted in the "context of clinical, radiographic, and cytologic features of each individual patient". In addition, NCCN panel state that a majority of the panelists would recommend BRAF V600E testing in the evaluation of follicular lesions. They also highlight that the diagnostic utility of molecular diagnostics in pediatric patients is still unclear because most of the published literature is on adult patients with thyroid nodules. If the result of the specific molecular test in conjunction with clinical and ultrasound features result in a predicted risk of malignancy that is comparable to the rate seen in cytology benign thyroid FNA (approximately <5%), panelists recommend to follow patients with observation rather than proceeding to surgical resections.

American Thyroid Association (ATA)

The 2015 ATA guidelines on the management of adult patients with thyroid nodules and differentiated thyroid cancer make the following recommendations on the use of molecular markers (Haugen et al., 2016):

- If molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing and about the possible uncertainties in the therapeutic and long-term clinical implications of results. (Strong recommendation; low-quality evidence)
- If intended for clinical use, molecular testing should be performed in Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or the international equivalent, because reported quality assurance practices may be superior compared to other settings. (Strong recommendation; low-quality evidence)
- For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (Weak recommendation; moderate-quality evidence)
- Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (Weak recommendation; moderate-quality evidence)

The guidelines also state that "there is currently no single optimal molecular test that can definitively rule in or rule out malignancy in all cases of indeterminate cytology, and long-term outcome data proving clinical utility are needed" (Haugen et al., 2016).

The ATA Guidelines Task Force on Pediatric Thyroid Cancer have developed unique guidelines for children and adolescents with thyroid tumors. They have presented 34 recommendations including recommendations on molecular markers testing and nodules. The ATA panel recommended the pediatric age to be limited to a patient that is $\leq$ 18 years of age to more accurately define the impact of the physiologic changes of growth and development on tumor behavior (Francis et al, 2015).

AACE/ACE/AME

Guidelines from the American Association of Clinical Endocrinologists, American College of Endocrinology (ACE) and Associazione Medici Endocrinologi (AME) recommend the following (Gharib et al., 2016):

- “Molecular testing should be considered to complement not replace cytologic evaluation, where the results are expected to influence clinical management.”
- “As a general rule, not recommended in nodules with established benign or malignant cytologic characteristics.”
- “Consider the detection of BRAF and RET/PTC and, possibly, PAX8/PPARG and RAS mutations if such detection is available.”
- “Because of the insufficient evidence and the limited follow-up, they do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate nodules.”
- “Currently, with the exception of mutations such as BRAFV600E that have a PPV approaching 100% for papillary thyroid carcinoma (PTC), evidence is insufficient to recommend in favor of or against the use of mutation testing as a guide to determine the extent of surgery”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81210, 81401, 81479, 81545

Code Number	PPA Required	PPA not Required	Not Covered
81210	X		
81401	X		
81479	X		
81545	X		
81599	X		
G9843	X		

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

1/1/2019	New policy developed. Molecular markers in fine needle aspirates of the thyroid is considered **medically necessary** for mutation analysis (Eg. BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or the use of gene expression classifier (Eg. Afirma GEC) in fine-needle aspirates of the thyroid that are cytologically characterized as follicular cell neoplasm (FN) / suspicious for follicular neoplasm (SFN), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) in adult patients (>18 years of age) being evaluated for thyroid carcinoma to assist in patient management decisions. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)